PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 519/06 — A1

(11) International Publication Number: **WO 00/32607**

(43) International Publication Date: 8 June 2000 (08.06.00)

(21) International Application Number: PCT/US99/27962

(22) International Filing Date: 24 November 1999 (24.11.99)

(30) Priority Data:
60/110,345 1 December 1998 (01.12.98) US

(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065–0907 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MILLER, Ross, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065–0907 (US). CEGLIA, Scott, S. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065–0907 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065–0907 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CRYSTALLINE SALTS OF A CARBAPENEM ANTIBIOTIC

(57) Abstract

Crystalline salts of an amorphous, unstable carbapenem antibiotic are obtained by formation of the besylate, tosylate, napsylate, saccharate or alizarate salt.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

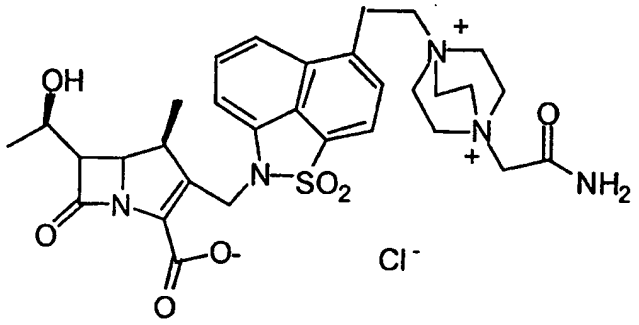
AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

TITLE OF THE INVENTION

CRYSTALLINE SALTS OF A CARBAPENEM ANTIBIOTIC

BACKGROUND OF THE INVENTION

The carbapenem antibiotic designated herein as Compound I:



I

is disclosed in U.S. Patent 5,756,725 (WO 97/40048) and has been shown to be a highly effective, broad spectrum antibiotic. However, formulation of this compound into a form suitable for the market place has been hampered by the unavailability of a stable crystalline form.

Prior to this invention, purification of Compound I was performed by column chromatography and the thermally and hydrolytically unstable amorphous chloride or triflate salt forms and their formulations had to be stored at low temperatures. Now with the present invention there are provided non-hygroscopic, thermally stable, crystalline salts readilly obtainable by a crystallization process which serves to purify the product as well, thus, avoiding the use of chromatographic techniques.

SUMMARY OF THE INVENTION

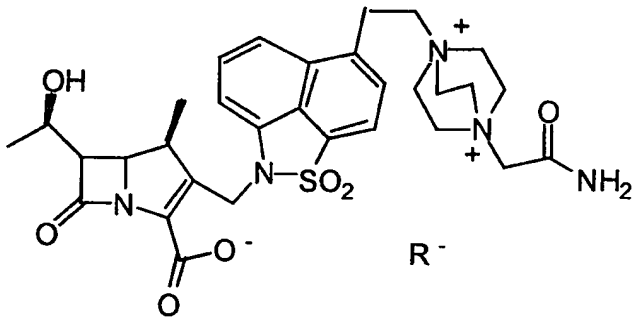
This invention is concerned with highly stable crystalline salts of Compound I and processes for their preparation, which processes incidentally serve to purify Compound I, especially by removal of palladium, ruthenium and tin contaminants.

The invention is also concerned with pharmaceutical formulations comprising one of the salts of Compound I as active ingredient.

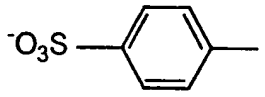
It is also concerned with a method of treating infections with the salts of this invention.

DETAILED DESCRIPTION OF THE INVENTION

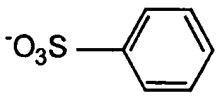
The Compound I salts of this invention are as shown below:



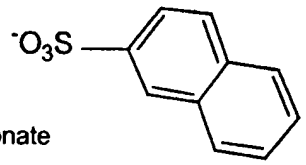
wherein R- is selected from:



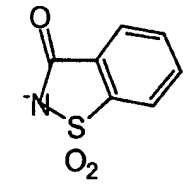
Tosylate



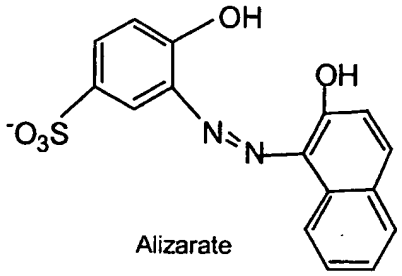
Benzensulfonate
"Besylate"



Naphthalenesulfonate
"Napsylate"



Saccharate



Alizarate

Each of these salt forming anions is well known in the art and known to be non-toxic and pharmaceutically acceptable.

A process for the preparation of the salts of this invention comprises treating a solution of Compound I with an alkali metal salt of formula M^+R^-, wherein M^+ is an alkali metal cation.. A group of alkali metal cations includes sodium(Na^+), potassium (K^+) and cesium (Cs^+). A sub-group includes Na^+ and K^+, and exemplary of this sub-group is Na^+.

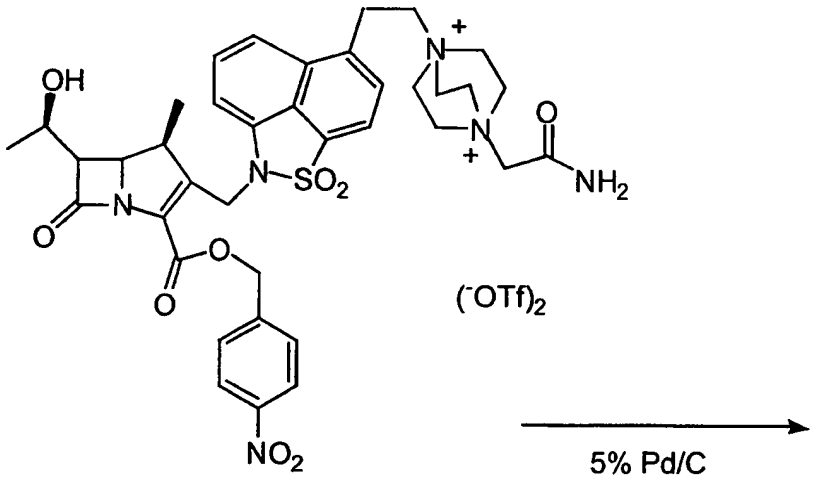
The counter ion associated with Compound I forming the starting material for the process of this invention includes any counter ion, X^-, that will provide a water soluble salt thereof. A group of such counter ions includes chloride, triflate, hemisulfate, mopsylate (4-morpholinepropanesulfonate), bromide, acetate and mesylate. A sub-group includes chloride and triflate. Exemplary of this sub-group is triflate.

The temperature at which the reaction is conducted is not critical. However, because of the limited stability of the Compound I starting material, the reaction temperature should be maintained at about 5 to about 25° C, and room temperature (about 15 to about 25° C) is convenient.

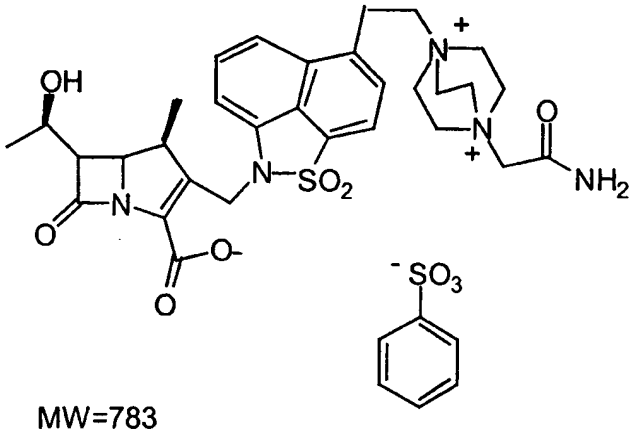
In one embodiment of the process of this invention, a solution of Compound I suitable for treatment with the alkali metal salt MR is obtained in the last step in the synthesis of Compound I which involves the hydrogenolysis of an activated ester of Compound I such as the p-nitrotoluyl , benzyl, allyloxy, or p-methoxybenzyl ester.

EXAMPLE

Hydrogenation of penultimate bis triflate and crystallization of the benzenesulfonate salt



MW=1058



MW=783

Materials	Amt.	Mole	MW
Penultimate Bis Triflate	5000g	4.73	1058
5% Pd/C	1250g		
Isopropanol	58L		
4-Morpholinepropanesulfonic acid	2971g	14.2	209.26
5N NaOH	1.42L	7.1	
Toluene	30L		
Water	126L		
Sodium Benzenesulfonate	12.5kg		

A buffered solution of 4-morpholinepropanesulfonic acid was prepared by dissolving 2941g in 58L water followed by addition of approximately 1.4L 5N NaOH, resulting in a final solution pH of 7.2.

This solution was then added to 5000g of penultimate bis triflate, and then 58L isopropanol was added. The resulting pH of the slurry was 6.9

The mixture was degassed and then 1250g 5% Pd/C added and the system placed under hydrogen (40psi) until the reaction was done. The resulting pH of the solution after reaction was 6.3.

The catalyst was filtered off and the cake slurry washed with 25L water. The filtrate was immediately cooled to 5° C to improve the stability of the Compound I cation.

The filtrate was washed with toluene (25L) and the layers separated. The separation was done at 5-10° C, gave a clean cut, but required a 15 minute age to settle.

The washed filtrate was added to a solution of sodium benzenesulfonate (12.5kg) in 37.5L water at 20° C.

The filtrate and aqueous sodium benzenesulfonate were added via a syringe equipped with a 0.45 um syringe filter to remove nefloss. The pH of the aq. sodium benzenesulfonate solution was checked before adding the washed filtrate and adjusted to 6.3 with an appropriate amount of 0.002M TfOH solution.

The resulting slurry was cooled to 5°C and filtered, slurry washed with1:1 IPA:water and then water.

The solid was dried under nitrogen at ambient temperature.

Employing the procedure substantially as described in the above EXAMPLE, but substituting for the sodium benzenesulfonate used therein, an equimolar amount of an alkali metal salt of an ion, R^-, wherein R^- is selected from tosylate, napsylate, saccharate and alizarate, there was produced the corresponding salt of Compound I.

A comparison of the stabilities of certain of the crystalline salts of this invention and certain amorphous salts is shown in the following Table;

TABLE

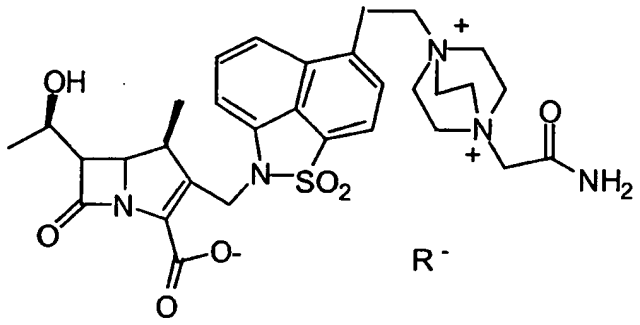
COMPOUND	INCREASE IN A% TOTAL IMPURITIES	DECOMPOSITION RATE A% / HR
Compound I chloride 30 min. @ 80° C	0.8	1.6
Compound I hemi-sulfate 25 min @ 80° C 120 min @ 80° C	1.1 5.4	2,7
Compound I besylate 120 min @ 120° C	0.05	0.03
Compound I saccharate 60 min @ 80° C	0.15	0.15

As can be seen from the Table, the normal decomposition rate of the lyophilized chloride solid is about 1.6A% per hour at 80° C. The hemisulfate is somewhat less stable at this temperature. However, in complete contrast, the benzenesulfonate is remarkably stable even at 100° C for 2 hours (less than 0.03A% degradation per hour).

Additionally, the besylate is non-hygroscopic at 20, 40, 60 and 90% humidity over 1 week.

WHAT IS CLAIMED:

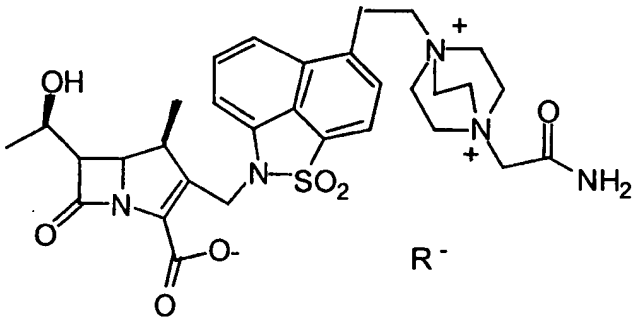
1. A compound of structural formula:



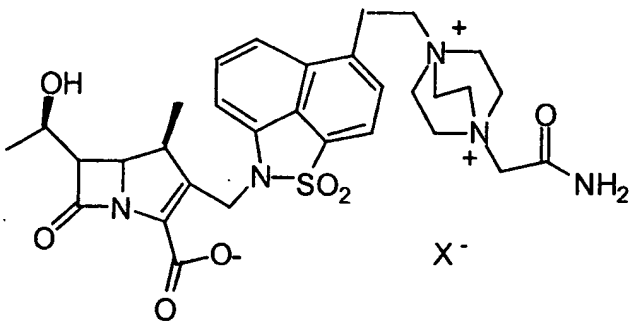
wherein R- represents besylate, tosylate, napsylate, saccharate or alizarate.

2. The compound of Claim 1 wherein R- represents besylate.

3. A process for the preparation of the compound of formula:



wherein R- represents besylate, napsylate, tosylate, saccharate and alizarate,which comprises treating an aqueous solution of a starting material of formula:

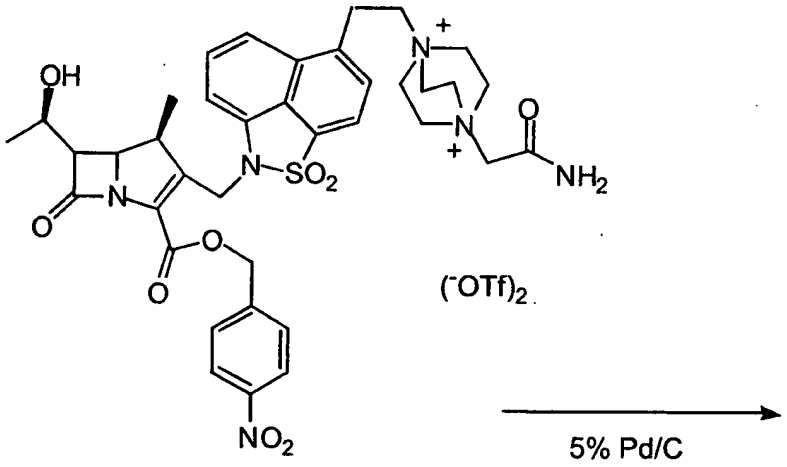


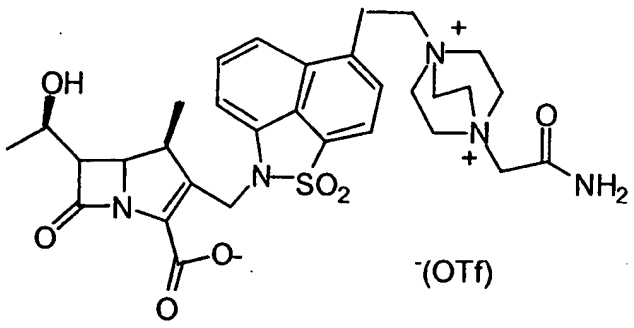
wherein X^- is a counter ion that provides water solubility to the starting material.

4, The process of Claim 3 wherein the X^- is chloride, triflate, hemisulfate, mopsylate, bromide, mesylate or acetate.

5. The process of Claim 4, wherein X^- is triflate.

6. The process of Claim 5 wherein the starting material is obtained from the final step of the process for the synthesis of Compound I comprising the hydrogenolysis of an activated ester as follows:




OH
N
O
O
O-
N
SO2
N
+
N
+
O
NH2
-(OTf)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/27962

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :C07D 519/06
US CL :540/302
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 540/302

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,756,725 A (WILKENING et al) 26 May 1998(26.05.98), see column 6, line 1.	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 JANUARY 2000	14 APR 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MARK L. BERCH Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*